

Recombinant factor VIIa to prevent surgical bleeding in factor XI deficiency

N. M. O'CONNELL, A. F. RIDDELL, G. PASCOE, D. J. PERRY and C. A. LEE

The Katharine Dormandy Haemophilia Centre and Haemostasis Unit, The Royal Free & University College Medical School, London, UK

Summary. Factor XI (FXI) deficiency is associated with bleeding after invasive procedures. Risks of human plasma-derived FXI replacement products include transfusion transmitted infection, thrombosis and fluid overload. This study was designed to test the hypothesis that recombinant factor VIIa (rFVIIa) is an effective haemostatic agent in patients with FXI deficiency undergoing surgery. Fourteen FXI deficient patients [five severely deficient (FXI:C <20 U dL⁻¹) and nine partially deficient (FXI:C 20–70 U dL⁻¹) received rFVIIa to prevent surgical bleeding during five major, four minor and six dental procedures. Minor surgical and dental procedures were covered with two doses of rFVIIa (90 µg kg⁻¹ i.v.), the first pre-operatively and the second 4 h postoperatively. Major surgery was covered with 90 µg kg⁻¹ i.v. two hourly for the first 24 h and four

hourly for the second 24 h. Oral tranexamic acid was given for 7 days postoperatively. Effective haemostasis was observed in all cases and no alternative haemostatic agents or blood transfusions were required. Three adverse events were recorded; an acute cerebrovascular accident in a patient with a history of cardiovascular disease, an allergic reaction and local phlebitis. In this study, rFVIIa was an effective alternative to plasma-derived FXI replacement for the prevention of surgical bleeding in FXI deficient patients but rFVIIa may not be suitable for patients with pre-existing risk factors for thrombosis.

Keywords: factor XI deficiency, recombinant factor VIIa, surgery, thrombin generation, thromboelastography

Introduction

Factor XI (FXI) deficiency is a rare bleeding disorder but is relatively frequent in persons of Ashkenazi Jewish descent where it occurs at a frequency of 8% [1]. Severely deficient patients have a FXI coagulant activity (FXI:C) of <20 U dL⁻¹ (reference range 70–150 U dL⁻¹), while partially deficient patients have FXI:C of 20–70 U dL⁻¹ [2,3]. The disorder is char-

acterized by bleeding associated with invasive procedures rather than by spontaneous bleeding and by a marked variability in the bleeding tendency [3]. The majority of patients with severe FXI deficiency have a history of bleeding after invasive procedures but within this group there are individuals with no bleeding symptoms despite adequate haemostatic challenge [3]. Postoperative bleeding is reported in 31–59% of partially deficient patients and is unrelated to the FXI:C level [4]. Factors which influence the likelihood of bleeding include the site of the surgical procedure and the clinical bleeding phenotype after previous haemostatic challenges [5].

Currently available therapy for FXI deficiency consists of antifibrinolytic agents and/or FXI replacement either with solvent-detergent-treated fresh frozen plasma (SD FFP) or FXI concentrate [6]. The decision to use any of these agents is an empiric one and is usually based on the severity of the deficiency, the previous clinical bleeding history and the site of the proposed invasive procedure. Of the

Present address: Prof Christine A. Lee, Haemophilia and Thrombosis Centre, Churchill Hospital, Old Road, Headington, Oxford OX3 7LJ, UK.

Present address: Dr David Perry, Department of Haematology, Box 234, Addenbrookes hospital, Hills Road, Cambridge CB2 2QQ, UK.

Correspondence: Dr N. M. O'Connell, Department of Haematology, The Adelaide and Meath Hospital, Tallaght, Dublin 24, Ireland.

Tel.: +353 1 4143966; fax: +353 1 4145908;
e-mail: niamh.oconnell@amnch.ie

Accepted after revision 17 January 2008

antifibrinolytic agents, tranexamic acid is most commonly used and is especially useful in surgery with increased fibrinolysis such as the oral cavity and for minor surgical procedures [7]. FXI concentrate is the FXI replacement of choice for major surgical procedures but it has been associated with activation of the coagulation cascade and thromboembolic side effects, which limits its use to patients without pre-existing risk factors for thrombosis [4,8–12]. FXI concentrate is manufactured in the UK and France and is available on a named patient basis only [13,14]. Outside of these countries, the most commonly used FXI replacement is SD FFP which contains FXI in addition to a large number of other plasma proteins. Allergic reactions to the additional plasma proteins can occur and the volume load inherent in this treatment may be contra-indicated in some patients. In addition, treatment with SD FFP is unlikely to normalize FXI:C levels in severely deficient patients. All of the currently available FXI replacement products are plasma derived and although viral inactivation steps are included in the manufacturing process, the potential for transfusion transmitted infection is still present.

An alternative treatment option is required for FXI deficient patients. Ideally, treatment should be recombinant and capable of replacing the role of FXI in augmenting thrombin generation in the consolidation phase of coagulation [15–17]. Recombinant factor VIIa (rFVIIa; NovoSeven®; Novo Nordisk, Bagsvaerd, Denmark) fulfils these requirements, in particular because it generates a burst of thrombin on the surface of the activated platelet [18–20]. The use of rFVIIa in FXI deficiency was first reported in 1990 when rFVIIa was used to prevent surgical bleeding in a patient with an inhibitor to FXI undergoing orchidectomy [21]. Subsequently, a small number of case reports in patients with and without inhibitors have confirmed that rFVIIa is effective in preventing surgical haemorrhage [22–24]. This study was designed as a pilot study to extend the data on the use of rFVIIa in FXI deficient patients to a larger case series.

Materials and methods

Between November 2001 and December 2002, consecutive patients with FXI deficiency with a planned major, minor or dental procedure were recruited to the study. Treatment with rFVIIa was offered to patients who, in the opinion of their treating clinician, would require haemostatic cover with FXI concentrate (i.e. the presence of a previous history of bleeding, procedure likely to result in

bleeding, procedure with potential to result in bleeding in a critical area). Patient inclusion criteria were age > 18 years and severe (FXI:C <20 U dL⁻¹) or partial (FXI:C 20–70 U dL⁻¹) FXI deficiency or FXI deficiency with persistent high-responding inhibitors. Exclusion criteria were known hypersensitivity to rFVIIa, uncontrolled disseminated intravascular coagulation, a recent thromboembolic event (within 6 weeks) or treatment with any haemostatic agent within 48 h of the first dose of rFVIIa.

As a consequence of a thrombo-embolic adverse event after 6 months of patient recruitment, subsequent patients with a history of cardiovascular disease or with current angina or intermittent claudication were excluded. Informed consent was obtained in all cases and the protocol was approved by the Local Research Ethics Committee.

The first dose of rFVIIa was given immediately pre-operatively. A total of two doses (90 µg kg⁻¹) 4 h apart was given to patients undergoing minor or dental procedures. For major procedures, rFVIIa at a dose of 90 µg kg⁻¹ was given two hourly for the first 24 h and four hourly for the second 24 h. Oral tranexamic acid was given postoperatively for 7 days, once rFVIIa treatment had finished for minor and dental procedures and once the patient was taking oral intake for major procedures.

The primary endpoints were the clinical assessment of haemostasis and the recording of adverse events. Clinical haemostasis ratings were graded as effective, partially effective or ineffective [25]. Secondary endpoints were the use of additional haemostatic agents and the requirement for more than a two-unit red cell transfusion. All endpoints were evaluated immediately postoperatively in all cases. Further evaluations were performed 4 h postoperatively in patients undergoing minor or dental procedures and 8, 24 and 48 h postoperatively in patients undergoing major procedures.

Pre-operatively, blood was collected into citrate tubes (0.106 mol L⁻¹ trisodium citrate; SARSTEDT Monovette, Nümbrecht, Germany) for analysis of the prothrombin time, D-dimers and FVII:C. The coagulation tests were repeated 15 min after the first dose of rFVIIa and pre and post the 2 or 4 h dose in the case of major or minor/dental surgery respectively. Patients undergoing major surgery also had these coagulation tests repeated pre and post the 24 and 48 h doses.

Thromboelastography (TEG) and a thrombin generation assay were also performed in a subgroup of samples where plasma was available [26,27]. The thrombin generation assay was performed on plasma which had been double spun and stored at –80°C

until assayed. Briefly, plasma was thawed and defibrinated with Reptilase, coagulation was initiated with recombinant tissue factor at a concentration of 10 pg mL⁻¹ and calcium. Subsampling from the test sample was performed at 30-s intervals into a stop solution containing EDTA and thrombin generation was determined by adding the chromogenic substrate S2238 and reading the absorbance at 405 nm. Calculations of peak thrombin and area under the curve (AUC) were performed with reference to a standard curve generated using dilutions of bovine thrombin (starting concentration 1000 U mL⁻¹).

Results

Fourteen patients were recruited to the study and fifteen surgical or dental procedures were performed. Patient characteristics including severity of FXI deficiency, prior bleeding history and procedure type are given in Table 1. One patient (patient 14) had a high responding inhibitor to FXI. Inhibitors to FXI were not detected in the remaining patients.

Haemostasis was classified as effective at all time points in all patients. No patient required an additional haemostatic agent or surgical intervention for unexpected haemorrhage and no red cell transfusions were given. One female patient, who underwent breast symmetrization, had a decrease in haemoglobin from 11.4 g dL⁻¹ pre-operatively to 9.5 g dL⁻¹

postoperatively and was given postoperative iron supplementation.

The prothrombin time shortened from a mean of 13.6 to 8.2 s (reference interval 12.9–13.9 s) after the first dose of rFVIIa and remained below the lower limit of the reference interval at all time points in all patients. FVII:C increased after administration of rFVIIa but there was considerable inter-individual variation (Fig. 1). The median FVII:C level post the first dose of rFVIIa was 44 U mL⁻¹ with a range of 28–65 U mL⁻¹. The trough level prior to the next dose was >6 U mL⁻¹ in all cases with a range of 11–26 U mL⁻¹ in major cases and 7–13 U mL⁻¹ in minor cases. The thromboelastogram was evaluated pre and post rFVIIa in nine patients (four severely deficient and five partially deficient). All patients had a prolonged *k* time and a reduced angle pre rFVIIa while six of nine patients had an abnormally prolonged *r* time (Table 2). The TEG parameters were corrected in all cases following therapy with rFVIIa.

Six patients (two severely deficient and four partially deficient) had thrombin generation in plasma measured before and after the first dose of rFVIIa (Table 2). The median AUC pre-rFVIIa was 2147.55 U mL⁻¹ (AUC of pooled normal plasma 2910.9 U mL⁻¹) which increased to 3804.55 U mL⁻¹ after rFVIIa. Peak thrombin increased from a median of 4.9 U mL⁻¹ to a median of 11.5 U mL⁻¹ after rFVIIa (pooled normal plasma 9.02 U mL⁻¹).

Table 1. Patient demographics and procedures.

Patient	Age	Gender	Baseline FXI:C	Bleeding history	Procedure	Classification of procedure
1	24	Male	9	Yes	Molar tooth extraction	Dental
2*	43	Female	44	Yes	Removal of titanium implant	Dental
3	42	Female	56	Yes	Repair of common extensor origin (elbow)	Major
4	77	Male	48	Yes	Bilateral herniorrhaphy	Major
5	31	Female	44	Yes	Endometrial ablation/bilateral salpingectomy/diathermy	Major
6*	43	Female	44	Yes	2 dental titanium implants	Dental
7	77	Male	3	Yes	Hydrocoele repair	Major
8	38	Male	39	No	Colonoscopy and biopsy	Minor
				(dental extractions)		
9	20	Female	45	Yes	Bone biopsy	Minor
10	25	Female	56	No	Breast symmetrization	Minor
				(dental extractions)		
11	37	Male	58	Yes	Vasectomy	Minor
12	43	Female	42	Yes	Extraction 3 impacted wisdom teeth	Dental
13	62	Male	10	Yes	Extraction 1 impacted molar tooth	Dental
14†	65	Female	1	Yes	Total hip replacement	Major
15	59	Male	11	No	Extraction 1 wisdom tooth and 1 molar tooth	Dental
				(tonsillectomy, circumcision)		

*Two procedures undertaken in the same patient; †This patient had a FXI inhibitor.

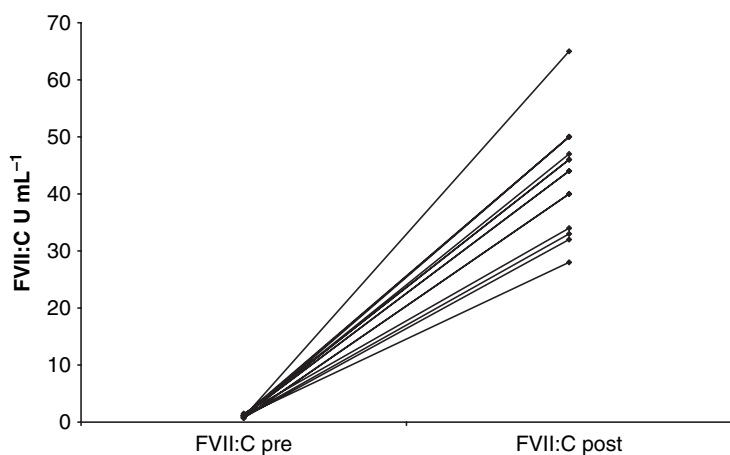


Fig. 1. FVII:C levels pre and post first dose of rFVIIa for all 15 procedures. All pre FVII:C levels were within the normal range ($0.5\text{--}1.5\text{ U mL}^{-1}$). Note that some patients had identical post rFVIIa FVII:C levels (three patients: 50 U mL^{-1} , two patients: 46 U mL^{-1} , two patients: 44 U mL^{-1} , two patients: 40 U mL^{-1}).

Table 2. Thromboelastography (TEG) and thrombin generation test (TGT) results pre and post the first dose of rFVIIa.

Test Parameter (Normal)	TEG						TGT			
	<i>r</i> time (14–23 s)		<i>k</i> time (3–7 s)		Angle (31–49)		AUC (2910.9 U mL^{-1})		Peak thrombin (9.0 U mL^{-1})	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Patient										
1	32	14.9	10.7	4.8	18.5	37.5	.	.	.	.
2	22.5	7.6	9.2	3	20.5	53.5	3365.2	3829.9	11.3	11.4
3	28.6	9.9	24.8	3.8	9	44.5	1990.4	3313.8	5.1	10.5
4	23.9	9.2	8.7	2.4	25	49.5	1402.5	4303.4	4.7	11.6
5	16.9	11.4	11.6	5.8	18.5	44	.	.	.	.
9	.	.	.	.	.	.	3884.4	4614.1	12.1	13.8
12	20.8	11.8	7.3	3.6	30	46	.	.	.	.
13	28	11.3	10.1	3.1	21	59	.	.	.	.
14	55.1	10.7	12.7	2.4	20.5	62	2304.7	3779.2	2.9	16.6
15	36.4	16.8	12.6	5.9	19	39.5	1333.9	2832.5	1.8	10.1

Three adverse events were documented during the study. A 77-year-old male patient (patient 7, Table 1), with a history of a myocardial infarction 8 years previously, developed clinical and radiological evidence of a cerebrovascular infarct after the 17th of 19 planned doses of rFVIIa and died 3 days later. The FVII:C levels obtained pre and post the first, second and 24 h rFVIIa doses were similar to other patients in the study on the same dosing regimen. The maximum FVII:C level obtained was 73 U mL^{-1} post the second dose of rFVIIa. D-Dimers became elevated in this patient at 24 h postoperatively, as occurred in all patients undergoing major procedures.

A 31-year-old female patient (patient 5, Table 1) with a strong history of atopy developed periorbital rash and itching associated with mildly elevated liver function tests. These symptoms resolved after discontinuation of treatment. Further investigations suggested an allergy to polysorbate 80, an excipient of rFVIIa.

A 42-year-old female patient (patient 3, Table 1) developed a mild local phlebitis, which resolved with conservative therapy.

Discussion

The management of surgical procedures in FXI deficient patients presents a particular challenge to clinicians because of the variability of bleeding between individuals and within a single individual in response to different haemostatic challenges. At present, the decision to give FXI replacement, an antifibrinolytic agent or no treatment is an empiric one and is dependent on the prior bleeding phenotype. The level of FXI coagulant activity also plays a role in the decision to treat because patients with $\text{FXI:C} < 20\text{ U dL}^{-1}$ have a increased likelihood of bleeding although this is not universal even at low FXI levels. While antifibrinolytic therapy is useful, single agent tranexamic acid may not always be suitable cover for major procedures or for severely

deficient patients. In these circumstances, FXI replacement with human plasma-derived SD FFP or FXI concentrate is indicated. SD FFP and FXI concentrate are associated with a number of adverse effects, including volume overload, allergic reactions, thrombosis and exposure to human plasma.

There is no recombinant FXI replacement product under development at the present time. The efficacy and safety of rFVIIa is well established in the management of acute bleeds and invasive procedures in patients with severe FVIII or FIX deficiency and inhibitors. Inhibitors to FXI have been well described and are associated with severe FXI deficiency and exposure to plasma-derived FXI [28]. There was an early report of the use of rFVIIa ($60 \mu\text{g kg}^{-1}$ three hourly for 3 days) in a patient with FXI deficiency and a FXI inhibitor undergoing an orchidectomy for testicular haemorrhage [21]. A number of case reports subsequently documented the use of rFVIIa in FXI deficiency and inhibitors [22–24]. Doses used ranged from 30 to $90 \mu\text{g kg}^{-1}$. At the time that this study was designed and conducted, there were no other available data on the use of rFVIIa in patients with FXI deficiency. The dose of $90 \mu\text{g kg}^{-1}$ used in this study was chosen because there was extensive experience in prevention of bleeding in haemophilic patients undergoing surgical procedures at this dose [29]. There is also laboratory evidence that the haemostatic dose of rFVIIa is $>70 \mu\text{g kg}^{-1}$ [30].

Tranexamic acid has been used safely with rFVIIa in severe haemophilia with inhibitors. In this study, the additional use of tranexamic acid was deemed necessary because the period of cover with rFVIIa was limited to the immediate postoperative period and tranexamic acid was used to prevent late bleeding.

Thromboembolic adverse events are uncommon but recognized adverse event associated with therapeutic use of activated clotting factors [31]. In common with other reports, the patient affected by a cerebrovascular accident in this study had pre-existing risk factors. Following this experience, the protocol was modified and subsequent patients were excluded if risk factors for thromboembolic disease were present. Patients with FXI deficiency do not appear to be inherently protected from arterial thrombosis by their coagulation factor deficiency [32]. Therefore, rFVIIa should be used with caution in such patients. More recently, reports have suggested that much lower doses of rVIIa, analogous to those used in FVII deficiency, may be effective in achieving haemostasis in FXI deficiency [33,34]. In the first of these case reports, Brown noted that a single dose of $12 \mu\text{g kg}^{-1}$ was sufficient to arrest a postpartum haemorrhage, while Schulman and

Nemeth reported the use of bolus doses of $29 \mu\text{g kg}^{-1}$ and $18 \mu\text{g kg}^{-1}$ and continuous infusion rates of $1.1\text{--}3.6 \mu\text{g kg}^{-1} \text{ h}^{-1}$ to prevent surgical bleeding during two separate spinal procedures in a single patient. These alternative dosing schedules merit further study in larger groups of patients.

As the mechanism of action of rFVIIa is not replacement of a deficient coagulation factor, the optimal monitoring method is unclear [35–37]. Levels of FVII:C reach supra-physiological levels after therapeutic doses of rFVIIa and *in vitro* data suggest that haemostasis occurs if FVII:C levels are maintained at $>6 \text{ U mL}^{-1}$ for several hours [30]. Clinical studies have revealed considerable inter-individual variation in FVII:C levels and the peak level of FVII:C is now felt to be the critical factor in promoting normal clot structure and maintaining haemostasis in patients with haemophilia [38,39]. In this study, all patients studied achieved peak FVII:C levels of $>25 \text{ U mL}^{-1}$ after one dose of rFVIIa. Trough levels were $>6 \text{ U mL}^{-1}$, both with two hourly and four hourly bolus dosing (data not shown), which correlated with satisfactory haemostatic efficacy in all cases. Lower target FVII:C levels may be effective in patients with FXI deficiency as documented in a recent case report [34].

Defective thrombin generation in FXI deficient patients causes inadequate activation of thrombin activatable fibrinolysis inhibitor (TAFI) and a consequent increase in fibrinolysis [40]. This correlates with the clinical observation of increased bleeding in areas of high fibrinolytic activity in patients with FXI deficiency [41]. In patients with severe haemophilia A, *in vitro* studies have demonstrated that rFVIIa inhibits fibrinolysis via TAFI and the concentration of rFVIIa required shows considerable individual variation, mirroring the variability seen in FVII:C *in vivo* [17]. Generation of thrombin at normal or supra-normal levels posttherapy with rFVIIa is suggested by the normalization of the TEG parameters in patients in this study and by the marked increase in the AUC and peak thrombin levels in the thrombin generation assay. Increased thrombin is postulated to lead to enhanced activation of TAFI with consequent downregulation of fibrinolysis.

Conclusion

In this pilot study, rFVIIa in combination with postoperative tranexamic acid was successful in preventing surgical bleeding. The use of a recombinant product to prevent surgical bleeding in FXI deficiency is especially desirable in younger patients,

children and pregnant women, in view of emerging risks of transfusion including new variant Creutzfeldt Jakob disease [42,43]. Caution is required when considering patients with pre-existing risk factors for thrombosis including atherosclerosis and rFVIIa should only be used in this patient group if the benefit of treatment clearly outweighs the risk of thrombosis. It is as yet unclear whether lower total doses of rFVIIa and lower target FVII:C levels will reduce this risk. Randomized studies are needed to determine the optimum dose and dose schedule of rFVIIa and tranexamic acid in patients with FXI deficiency undergoing invasive procedures.

Acknowledgements

This study was supported by a grant from the Special Trustees of the Royal Free Hospital and by the The Katharine Dormandy Trust for Haemophilia and related disorders, charity number 262434. Novo Nordisk (UK) Ltd supplied recombinant factor VIIa for use in the study.

Disclosures

Novo Nordisk (UK) Ltd has given unrestricted educational grants to the Katharine Dormandy Haemophilia Centre and Haemostasis Unit. N O'C has received speakers fees from Novo Nordisk (UK) Ltd. The authors are solely responsible for data analysis and interpretation and the content of the manuscript.

References

- 1 Seligsohn U. Factor XI deficiency. *Thromb Haemost* 1993; **70**: 68–71.
- 2 Bolton-Maggs PH, Young Wan-Yin B, McCraw AH, Slack J, Kernoff PB. Inheritance and bleeding in factor XI deficiency. *Br J Haematol* 1988; **69**: 521–8.
- 3 Bolton-Maggs PH, Patterson DA, Wensley RT, Tuddenham EG. Definition of the bleeding tendency in factor XI-deficient kindreds – a clinical and laboratory study. *Thromb Haemost* 1995; **73**: 194–202.
- 4 Collins PW, Goldman E, Lilley P, Pasi KJ, Lee CA. Clinical experience of factor XI deficiency: the role of fresh frozen plasma and factor XI concentrate. *Haemophilia* 1995; **1**: 227–31.
- 5 Brenner B, Laor A, Lupo H, Zivelin A, Lanir N, Seligsohn U. Bleeding predictors in factor-XI-deficient patients. *Blood Coagul Fibrinolysis* 1997; **8**: 511–5.
- 6 Bolton-Maggs PH. The management of factor XI deficiency. *Haemophilia* 1998; **4**: 683–8.
- 7 Berliner S, Horowitz I, Martinowitz U, Brenner B, Seligsohn U. Dental surgery in patients with severe factor XI deficiency without plasma replacement. *Blood Coagul Fibrinolysis* 1992; **3**: 465–8.
- 8 Smith JK. Factor XI deficiency and its management. *Haemophilia* 1996; **2**: 128–36.
- 9 Mannucci PM, Bauer KA, Santagostino E *et al.* Activation of the coagulation cascade after infusion of a factor XI concentrate in congenitally deficient patients. *Blood* 1994; **84**: 1314–9.
- 10 Gitel SN, Varon D, Schulman S, Martinowitz U. Clinical experiences of a FXI concentrate; possible side-effects. *Thromb Haemost* 1991; **65**: 1157.
- 11 Bolton-Maggs PH, Colvin BT, Satchi G, Lee CA, Lucas GS. Thrombogenic potential of factor XI concentrate. *Lancet* 1994; **344**: 748–9.
- 12 Briggs NJ, Harman C, Dash CH. A decade of experience with a factor XI concentrate. *Haemophilia* 1996; **2**(Suppl.1): 13.
- 13 Bolton-Maggs PH, Wensley RT, Kernoff PB *et al.* Production and therapeutic use of a factor XI concentrate from plasma. *Thromb Haemost* 1992; **67**: 314–9.
- 14 Burnouf-Radosevich M, Burnouf T. A therapeutic, highly purified factor XI concentrate from human plasma. *Transfusion* 1992; **32**: 861–7.
- 15 von dem Borne PA, Meijers JC, Bouma BN. Feedback activation of factor XI by thrombin in plasma results in additional formation of thrombin that protects fibrin clots from fibrinolysis. *Blood* 1995; **86**: 3035–42.
- 16 von dem Borne PA, Bajzar L, Meijers JC, Nesheim ME, Bouma BN. Thrombin-mediated activation of factor XI results in a thrombin-activatable fibrinolysis inhibitor-dependent inhibition of fibrinolysis. *J Clin Invest* 1997; **99**: 2323–7.
- 17 Lisman T, Mosnier LO, Lambert T *et al.* Inhibition of fibrinolysis by recombinant factor VIIa in plasma from patients with severe hemophilia A. *Blood* 2002; **99**: 175–9.
- 18 Hoffman M, Monroe DM III, Roberts HR. Activated factor VII activates factors IX and X on the surface of activated platelets: thoughts on the mechanism of action of high-dose activated factor VII. *Blood Coagul Fibrinolysis* 1998; **9**(Suppl. 1): S61–5.
- 19 Monroe DM, Hoffman M, Allen GA, Roberts HR. The factor VII-platelet interplay: effectiveness of recombinant factor VIIa in the treatment of bleeding in severe thrombocytopathia. *Semin Thromb Hemost* 2000; **26**: 373–7.
- 20 Kjalke M, Ezban M, Monroe DM, Hoffman M, Roberts HR, Hedner U. High-dose factor VIIa increases initial thrombin generation and mediates faster platelet activation in thrombocytopenia-like conditions in a cell-based model system. *Br J Haematol* 2001; **114**: 114–20.
- 21 Hedner U. Factor VIIa in the treatment of haemophilia. *Blood Coagul Fibrinolysis* 1990; **1**: 307–17.
- 22 Lawler P, White B, Pye S *et al.* Successful use of recombinant factor VIIa in a patient with inhibitor

- secondary to severe factor XI deficiency. *Haemophilia* 2002; 8: 145–8.
- 23 Musso R, Cultrera G, Giuffrida G, Fichera E, Di Francesco F, Salemi S. Recombinant activated factor VIIa as haemostatic agent in homozygous factor XI deficient patients. *Thromb Haemost* 2001; XVIII ISTH congress (abstract P1133) Available at <http://www.med.unc.edu/isth> (last accessed 03.03.08).
- 24 Billon S, Niger CL, Escoffre-Barbe M, Vicariot M, Abgrall JF. The use of recombinant factor VIIa (NovoSeven(R)) in a patient with a factor XI deficiency and a circulating anticoagulant. *Blood Coagul Fibrinolysis* 2001; 12: 551–3.
- 25 Shapiro AD. Recombinant factor VIIa in the treatment of bleeding in hemophilic children with inhibitors. *Semin Thromb Hemost* 2000; 26: 413–9.
- 26 Salooja N, Perry DJ. Thromboelastography. *Blood Coagul Fibrinolysis* 2001; 12: 327–37.
- 27 Hemker HC, Beguin S. Endogenous thrombin potential. In: Jespersen J, Bertina RM, Haverkate F, eds. *Laboratory Techniques in Thrombosis – A Manual*. Dordrecht, The Netherlands: Kluwer Academic Publishers, 1999: 63–78.
- 28 Salomon O, Zivelin A, Levnat T *et al*. Prevalence, causes and characterization of factor XI inhibitors in patients with inherited factor XI deficiency. *Blood* 2003; 101: 4783–8.
- 29 Hedner U, Erhardtsen E. Potential role for rFVIIa in transfusion medicine. *Transfusion* 2002; 42: 114–24.
- 30 Hedner U. Dosing and monitoring NovoSeven treatment. *Haemostasis* 1996; 26(Suppl. 1): 102–8.
- 31 Aledort LM. Comparative thrombotic event incidence after infusion of recombinant factor VIIa versus FVIII inhibitor bypass activity. *J Thromb Haemost* 2004; 2: 1700–8.
- 32 Salomon O, Steinberg DM, Dardik R *et al*. Inherited factor XI deficiency confers no protection against acute myocardial infarction. *J Thromb Haemost* 2003; 1: 658–61.
- 33 Brown SA. What dose of recombinant activated factor VII should be used in patients with factor XI deficiency? *Haemophilia* 2005; 11: 430–1.
- 34 Schulman S, Nemeth G. An illustrative case and a review on the dosing of recombinant factor VIIa in congenital factor XI deficiency. *Haemophilia* 2006; 12: 223–7.
- 35 Ingerslev J, Christiansen K, Calatzis A, Holm M, Sabroe Ebbesen L. Management and monitoring of recombinant activated factor VII. *Blood Coagul Fibrinolysis* 2000; 11(Suppl. 1): S25–30.
- 36 Cid AR, Lorenzo JI, Haya S, Montoro JM, Casana P, Aznar JA. A comparison of FVII:C and FVIIa assays for the monitoring of recombinant factor VIIa treatment. *Haemophilia* 2001; 7: 39–41.
- 37 Johannessen M, Nielsen G, Nordfang O. Comparison of the factor VII:C clot analysis and a modified activated factor VII analysis for monitoring factor VII activity in patients treated with recombinant activated factor VII (NovoSeven). *Blood Coagul Fibrinolysis* 2000; 11(Suppl. 1): S159–64.
- 38 He S, Blomback M, Jacobsson EG, Hedner U. The role of recombinant factor VIIa (FVIIa) in fibrin structure in the absence of FVIII/FIX. *J Thromb Haemost* 2003; 1: 1215–9.
- 39 Ludlam CA, Smith MP, Morfini M, Gringeri A, Santagostino E, Savidge GF. A prospective study of recombinant activated factor VII administered by continuous infusion to inhibitor patients undergoing elective major orthopaedic surgery: a pharmacokinetic and efficacy evaluation. *Br J Haematol* 2003; 120: 808–13.
- 40 Bouma BN, Meijers JC. Role of blood coagulation factor XI in downregulation of fibrinolysis. *Curr Opin Hematol* 2000; 7: 266–72.
- 41 Salomon O, Steinberg DM, Seligsohn U. Variable bleeding manifestations characterize different types of surgery in patients with severe FXI deficiency enabling parsimonious use of replacement therapy. *Haemophilia* 2006; 12: 490–3.
- 42 Llewelyn CA, Hewitt PE, Knight RS *et al*. Possible transmission of variant Creutzfeldt-Jakob disease by blood transfusion. *Lancet* 2004; 363: 417–21.
- 43 Peden AH, Head MW, Ritchie DL, Bell JE, Ironside JW. Preclinical vCJD after blood transfusion in a PRNP codon 129 heterozygous patient. *Lancet* 2004; 364: 527–9.